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| EXAMINER | |
|---|---|
| IBRAHIM, MEDINA AHMED | |
| ART UNIT | PAPER NUMBER |
| 1638 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/978,274 | THOMAS ET AL. | |
| | Examiner | Art Unit | |
| | MEDINA A. IBRAHIM | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *46-55,57 and 59-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *47-49,51,53-55,57,59 and 63-69* is/are allowed.

6)☒ Claim(s) *46,61,62,70 and 71* is/are rejected.

7)☒ Claim(s) *50,52 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Applicant's response filed 12/10/07 has been entered. Claims 46-47, 50-53, 59-63, and 66-69 are amended. Claim 58 is cancelled. Claims 70-71 are added. Therefore, claims 46-55, 57, and 59-71 are pending and are examined. The IDS filed 12/10/07 has been considered. An initialed and dated copy of the 1449 form is attached to this Office action.

3. All previous objections and rejections not set forth below have been withdrawn in view of Applicant's amendment and/or upon further consideration.

***Claim Objections***

Claim 52 is objected to for failing to further limit parent claim 51 because the Pro-PAP-S protein does not further limit SEQ ID NO: 2 because the specification indicates that Pro-PAP-S cannot be other than SEQ ID NO: 2. This objection is repeated for the reasons of record as set forth in the last Office action of 07/05/07. In the response of 12/10/07, Applicant has neither amended nor argued against the objection.

Claims 50 and 60 are objected to for reciting "pro-PAP-S". It is suggested that "a pro-PAP-S" protein be replaced with ---SEQ ID NO: 2-- (see the objection to claims 51, 58, 66-69, in the last Office action of 07/05/2007; claims 50 and 60 were inadvertently omitted in the objection).

***Claim Rejections - 35 USC § 112***

Claims 46, 61-62, and 70-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing cell death in specific cells in a plant by introducing a chimeric gene comprising the pokeweed antiviral protein (PAP) encoding sequences of SEQ ID NO: 1, 5, or 7 under the control of a nematode inducible promoter in a transgenic plant and SEQ ID NO: 3 in transgenic potato plants, and plants and plant cells produced by said method, does not reasonably provide enablement for a method of inducing cell death in any plant cells with a nucleic acid molecule encoding pokeweed antiviral protein having at least 70%, 80% or 90% homologous to SEQ ID NO: 2, 6 or 8. This rejection is repeated in part for the reasons of record as set forth in the last Office action of 07/05/07. Applicant's arguments filed 12/10/07 have been fully considered but are not deemed persuasive.

The claims are drawn to a method of inducing cell death in specific cells of a plant, said method comprising exposing a plant comprising a chimeric gene comprising a nucleic acid encoding pokeweed antiviral protein including Pro-PAP-S (SEQ ID NO: 2), PAP-S (SEQ ID NO: 4), PAP-S $\alpha$ (SEQ ID NO: 6) and PAP-S $\beta$ (SEQ ID NO: 8), under the control of a nematode inducible promoter, wherein the expression of said pokeweed antiviral protein induces cell death in said specific cells. The claims are also drawn to a method of inducing cell death in specific plant cells with a nucleic acid molecule encoding pokeweed antiviral protein having at least 70% homologous to SEQ ID NO: 2, 6 or 8 and capable of inducing cell death.

Applicant teaches constructs containing PAP-S nucleic acid sequences encoding SEQ ID NO: 2, 4, 6, and 8 under the control of 35S CaMV or a nematode inducible promoter for transient assay in tobacco protoplasts to show that PAP-S mediates ribosome inactivation (Figures 5-7). Applicant also teaches transformation of tobacco and potato with said constructs and expression of Pro-PAP-S or matures PAP-S in nematode infected root cells. Applicant teaches that transformation of tobacco with Pro PAP-S encoding sequence and potato with mature PAP-S or Pro-PAP-S sequences produced transgenic tobacco and potato plants with nematode resistance (Figures 13-14). Applicant also teaches that transformation of tobacco cells with a nucleic acid encoding mature PAP-S (SEQ ID NO: 4) failed to produce transformed tobacco cells.

Applicant has not provided guidance for a method of inducing cell death in specific cells of a plant using a nucleic acid having 70%, 80% or 90% homology to SEQ ID NO: 2, 6 or 8 and capable of inducing cell death. Applicant has not taught how and where to modify the disclosed sequences while retaining the desired protein function. Therefore, Applicant has not provided guidance for modifications to SEQ ID NO: 1-2, 5-6, or 7-8 that resulted sequences having both the structural and functional limitations of the claims which can be used in the claimed methods.

While mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims. One skilled in the art would expect any tolerance to modification for a given DNA/protein to diminish with each further and additional modification or multiple substitutions/ deletions. One skilled in the art would have to make all possible nucleotide substitutions

and deletions in SEQ ID NO: 1-2, 5-6, or 7-8 and test all sequences that meets the structural limitations to determine which also meet the functional limitation. Therefore, absent specific guidance regarding which regions in SEQ ID NO: 1-2, 5-6, or 7-8 would tolerate modifications; one skilled in the art would have to all possible amino acid or nucleotide modifications including deletions and substitutions in SEQ ID NO: 1-2, 5-6 or 7-8 to determine which would tolerate modifications. One would also have to determine the ability of said sequences to induce cell death upon expression in a transgenic plant. These tests are considered excessive and undue, absent evidence to the contrary.

Nielson et al (Annu. Rev. Plant Physiol. Plant Mol. Biol. (2001), vol. 52, pp. 785-816, in record) teach about ribosome inactivating proteins including pokeweed, their enzymatic activities, and their complex biological role. Nielson et al specifically states that while plant RIPs have been linked to antiviral, antifungal and insecticidal activity in transgenic plants, the mechanism of these effects remains unresolved (see at least the Abstract on page 785). The paragraph bridging pages 801 and 802, the cited reference states "(a)lthough the enzymatic mechanism of RIP activity is well defined, the physiological steps by which ribosome inactivation leads to cell death are not well understood".

The prior art teaches that transformation of a plant with a PAP encoding nucleic acids is highly unpredictable. For example, Lodge et al (PNAS, vol. 90, pp.7089-7093, 1993, Applicant's IDS) teach that the expression of PAP in transgenic plants may result undesired phenotype such as stunted, molted and sterility in the plant. Lodge et al teaches that tobacco plants expressing high levels (above 10ng/mg of protein) of wild

type and mutant PAP tend to have stunted and mottled phenotype, and some the plants were sterile (see page 7090, Results and Discussion). On the other hand, Barbieri et al (Biochemica et Biophysica Acta, vol. 1154, pp. 237-282, 1993, Applicant's IDS) teaches that plant RIPs including PAP can act on their ribosome only at high levels of concentrations (see pages 251-252, section III-A). Another example is Tumer et al (PNAS, vol. 94, pp. 3866-3871, 1997, Applicant's IDS) who teach transgenic tobacco plants expressing high levels of PAP with point mutations showed growth reduction and lesions on their leaves (Fig. 3 on page 3868), while transgenic plants expressing high levels of active site mutant PAP didn't show antiviral activity, and while transgenic plants expressing low levels of C-terminal deletion mutant were resistant to virus and showed normal growth (Table 2, page 3870).

In addition, the working examples disclosed in the specification are limited to the use of unmodified nucleic acids encoding pro-PAP-S (SEQ ID NO: 2), PAP-S $\alpha$ (SEQ ID NO: 6), and PAP-S$\beta$ (SEQ ID NO: 8) in potato and tobacco. The ability of SEQ ID NO: 1-2, 5-6 or 7-8 to induce cell death in specific cells cannot be extrapolated to variants thereof having at least 70%, 80% or 90% homology to the disclosed sequence, absent further guidance.

Therefore, given the breadth of the claims, the state of the prior art; the nature of the invention; the limited working examples, and the unpredictability with respect to PAP activity in transgenic plants as discussed above, the claimed invention is not enabled throughout the broad scope. See In re Wands 858 F.2d 731, 8USPQ2nd 1400 (Fed. Cir, 1988).

***Response to Arguments***

Applicant asserts that the claims as amended would satisfy the enablement requirement of 35 USC 112, 1st paragraph. This is not found persuasive because the claims are amended to recite "nucleic acid encoding pokeweed antiviral protein having at least 70%, 80%, or 90% homology to SEQ ID NO: 2, 5 or 8. However, the instant specification does not support the broad scope of the claims for the reasons discussed above.

See also *Genentech Inc. v. Novo Nordisk* A/S (42 USPQ2d 1001 at p. 1005) where the CAFC stated "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not workable…While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention…[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required…. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". Id. In this case, as in *Genentech*, the specification does not provide the "reasonable detail ……to enable members of the public to understand and carry out the invention" as broadly claimed.

Given that the broad scope of the claims encompassing a method that employs a nucleic acid encoding PAP having 70%, 80% or 90% homology to SEQ ID NO: 2, 6 or

8 and capable of inducing cell death; the limited working examples; the unpredictability inherent in expressing PAP in a transgenic plant as evidenced by Lodge et al; Barbieri et al; and Applicant's own specification teaches that a method for expressing a mature PAP-S under the control of a inducible promoter failed to produce transgenic tobacco plant; and the complex biological function of RIPs as discussed above, the claimed invention is not enabled throughout the broad scope. Therefore, the rejection is maintained.

***Remarks***

The closest prior arts made of record and not relied upon are considered pertinent to Applicant's disclosure. Tumer et al (WO 99/60843, Applicant's IDS); Kanieswski et al (6, 015, 940); Thomas et al (US 6,140,554); Poyet et al (FEBS (1997) vol 409 no.1-2, pp. 97-100); and Stuart et al (Publication #199400712, Applicant's IDS of 12/10/07).

Tumer et al teach a method of producing transgenic plants expressing a chimeric gene comprising a nucleic acid encoding pokeweed antiviral protein and a promoter.

Thomas et al teach methods of producing *Meloidogne javanica* resistant transgenic plants with cell-specific promoters such as KNT1 and RB7 with cell-death system to disrupt the nematode feeding cells.

Kanieswski et al teach a method of inducing viral resistance in tobacco and potato plants and plant cells with a chimeric gene comprising a DNA sequence encoding PAP' or a mutant thereof retaining PAP activity, a tissue-specific or inducible promoter.

Poyet et al teach isolated and characterized nucleic acids encoding PAP-S including SEQ ID NO: 2, 4, 6, and 8.

Stuart et al teach a method of inducing a necrotic effect in a specific cell of a plant using a nucleic acid encoding cell necrotic molecule such as barnase under the control of a promoter that acts in response to a specific stimulus.

Tumer et al, Thomas et al, Kanieswski et al, Poyet et al, or Stuart et al, do not teach or suggest the use of PAP-S sequences under the control of inducible cell specific promoters such as KNT1 or RB7 to induce cell death in a transgenic plant.

***Remarks***

Claims 47-49, 51-59, 63-69 are allowable.

4. Claims 50, 52 and 60 would be allowable if the objection is above is obviated by replacing the "Pro-PAP-S" with ---SEQ ID NO: 2---.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

**Contact information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Medina A. Ibrahim whose telephone number is (571) 272-0797. The Examiner can normally be reached Monday -Thursday from 8:00AM to 5:30PM and every other Friday from 9:00AM to 5:00 PM. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.
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/Medina A Ibrahim/
Primary Examiner, Art Unit 1638

| Application Number | Application/Control No. | Applicant(s)/Patent under Reexamination | |
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| | 09/978,274 | THOMAS ET AL. | |
| | Examiner | Art Unit | |
| | MEDINA A. IBRAHIM | 1638 | |